REMARKS

I. Introduction

In response to the Office Action dated September 12, 2002, claims 10, 15, 16, 18, 24, 53, 55-57 and 69-70 have been cancelled, and claims 1, 7, 12, 17, 19-21, 33, 35-37, 41, 46, 48-51, 58-59, 66 and 71 have been amended. Claims 1-9, 11-14, 17, 19-23, 25-52, 54, 58-68 and 71 remain in the application. Reconsideration of the application, as amended, is requested.

II. Amendments to Claims and Specification

Applicants' attorney has made amendments to the claims as indicated above. In addition, the specification has been amended to correct obvious typographical errors. These amendments were made solely for the purpose of clarifying the language of the claims and specification, are supported by the application as originally filed, and do not introduce new matter. Entry of these amendments is respectfully requested.

III. Restriction Requirement

On page (2) of the Office Action, the restriction requirement raised in previous Office Actions was made final. Applicants respectfully request the Examiner reconsider rejoinder of at least some of the withdrawn claims upon identification of allowable subject matter. In this regard, Applicants note that all of the claims, as amended, now recite all 3 of agents i, ii, and iii.

IV. Non-Art Rejections

On page (2) of the Office Action, claims 1-7, 9-14, 20-23, 25, 59-63, 65-68, and 71 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

Applicants have amended claims 7, 20 and 71 to overcome this rejection. Amendment to claims 1, 23 and 24, however, is not required for the reasons discussed below.

Claim 1 was regarded as indefinite as to the intended analogs. Applicants respectfully direct the Examiner's attention to the specification at page 4, lines 24-27, which defines an "insulin analog" as "a peptide that has insulin-like physiological activity, i.e., binds an insulin receptor and lowers blood glucose, and that includes one or more amino acids different from the amino acid sequence of

a naturally occurring insulin." Specific examples of insulin analogs for use with the invention are described in the specification at page 5, line 26, to page 6, line 2. Accordingly, one skilled in the art would have no difficulty ascertaining the metes and bounds of the recited "insulin analogs".

Claim 1 was also regarded as indefinite because of the recitation of insulin related peptide. Applicant respectfully notes that "insulin related peptides" are defined in the specification at page 2, lines 1-3, as "peptides that are naturally secreted by the pancreas together with insulin in non-diabetics." Examples of such insulin related peptides are described in the specification at page 6, lines 3-9.. Accordingly, one skilled in the art would have no difficulty ascertaining the metes and bounds of the recited "insulin related peptides".

At page 2 of the Office Action, it was noted that the terms "GLP-1" and "IGF-1" may be used in claim 7 if accompanied by the full name that these abbreviations represent. Applicants have amended claim 7 accordingly.

Claims 20 and 71 were regarded as unclear in the recitation of "two or more compounds of agents, i, ii, or iii". Applicants have amended the claims to clarify that this phrase refers to two or more compounds within any one of the three recited groups of agents.

Claims 23 and 24 were considered to include a limitation not required by the claim from which they depend because they recite "further comprising" in connection with "a pharmaceutically acceptable carrier" in the case of claim 23 and "an insulin sensitizer" in the case of claim 24. Because claim 21 does not recite "a pharmaceutically acceptable carrier", Applicants are unclear as to the basis for this concern. Applicants respectfully note that "a pharmaceutically acceptable carrier" is distinct from the "pharmaceutically acceptable non-ionic surfactant" that coats the hydrophobic portion of agent iii) as recited in claim 21. The cancellation of claim 24 renders the rejection of this claim moot, but Applicants note that claim 21 also did not recite "insulin sensitizer" prior to the amendment presented herein.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

V. Prior Art Rejections

On page (3) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(e) as being anticipated by **Riveley, U.S. Patent No. 6,153,632** (Riveley). On page (4) of the Office

Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(e) as being anticipated by **Knudsen, U.S. Patent No. 6,268,343** (Knudsen). On page (4) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(a) as being anticipated by **Smith, WO 98/57636** (Smith). On page (4) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(b) as being anticipated by **Tomas, WO 96/02270** (Tomas). On page (4) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(b) as being anticipated by **Rink, WO 92/20366** (Rink). On page 5 of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(e) as being anticipated by **Clark, U.S. Patent No. 5,783,556** (Clark). On page (5) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(b) as being anticipated by **Cooper, U.S. Patent No. 5,641,744** (Cooper). On page (5) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(b) as being anticipated by **Froesch, U.S. Patent No. 4,988,675** (Froesch). On page (6) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(b) as being anticipated by **Chance, U.S. Patent No. 4,652,548** (Chance). On page (6) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §102(b) as being anticipated by **L'Italien, U.S. Patent No. 6,136,784** (L'Italien). On pages (6)-(7) of the Office Action, claims 1, 59, and 71 were rejected under 35 U.S.C. §103 as being unpatentable over **Habener, U.S. Patent No. 5,958,909** (Habener).

Applicants respectfully traverse these rejections in view of the amendments to the claims and the arguments discussed below.

Independent claims 1, 21, 41, 51, 58, and 59 are generally directed to compositions and methods for treating diabetes using a combination of 3 agents: (1) an insulin, an insulin analog, a physiologically active fragment of said insulin, a physiologically active fragment of said insulin analog and/or an insulin mimetic material; (2) an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and/or a physiologically active insulin-related peptide analog fragment; and (3) an insulin sensitizer.

The cited references do not teach nor suggest these various elements of Applicants' independent claims. More specifically, none of the cited references, taken alone or in combination, teach the use of all 3 agents recited in Applicants' claims.

Riveley merely describes an invention directed to a novel method and composition for the treatment of diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"]and Type II). More

specifically, this invention pertains to a novel method of treating diabetes mellitus by incorporating a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor for the treatment of diabetes mellitus. However, Riveley lacks any discussion about combining this therapy with insulin-related peptide therapy. Instead, Riveley teaches away from Applicants' invention because it teaches combining instead a hypoglycaemic agent such as sulfonylurea, biguanide or alpha-glucosidase inhibitor.

Knudsen merely describes an invention relating to GLP-1 derivatives having a lipophilic substituent, pharmaceutical compositions comprising same, and methods of making and using same, including compositions combining GLP-1 with insulin. Like Riveley, however, Knudsen lacks any discussion about combining the 3 agents of Applicants' claimed invention. Instead, Knudsen teaches away from Applicants' invention because it also teaches combining instead a hypoglycaemic agent, preferably an oral hypoglycaemic agent.

Similarly, each of the remaining cited references teaches combining only two of the 3 agents required by Applicants' claims, and lacks any teaching or suggestion to combine all 3 agents in a single therapeutic strategy. Even when combined, the references teach away from Applicants' invention. For example, the combined references would teach use of a conventional hypoglycaemic agent (agent such as sulfonylurea, biguanide or alpha-glucosidase inhibitor) as the third ingredient in a combination therapy.

Thus, Applicants submit that independent claims 1, 21, 41, 51, 58, and 59 are allowable over Riveley, Knudsen, Smith, Tomas, Rink, Clark, Cooper, Froesch, Chance, L'Italien, and Habener, either alone or in combination. Further, dependent claims 2-20, 22-40, 42-50, 52-57, and 60-71 are submitted to be allowable over Riveley, Knudsen, Smith, Tomas, Rink, Clark, Cooper, Froesch, Chance, L'Italien, and Habener in the same manner, because they are dependent on independent claims 1, 21, 41, 51, 58, and 59, respectively, and thus contain all the limitations of the independent claims. In addition, dependent claims 2-20, 22-40, 42-50, 52-57, and 60-71 recite additional novel elements not shown by Riveley, Knudsen, Smith, Tomas, Rink, Clark, Cooper, Froesch, Chance, L'Italien, and Habener.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §§102-103 be withdrawn.

VI. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

GATES & COOPER LLP
Attorneys for Applicant(s)

Howard Hughes Center
6701 Center Drive West, Suite 1050
Los Angeles, California 90045
(310) 641-8797

Date: December 10, 2002

By: _____
Name: Karen S. Canady
Reg. No.: 39,927

KSC/WJW/sjm/amb

G&C 130.32-US-01

APPENDIX: VERSION WITH MARKINGS
TO SHOW CHANGES MADE TO THE SPECIFICATION

Please replace the paragraph at page 1, line 25, to page 2, line 3, with the following paragraph:

Insulin and insulin analogs are commonly administered to diabetic patients, particularly Type 1 patients, in an injectable composition which comprises a pharmaceutically acceptable carrier and typically one or more conventional excipients. It is believed to be desirable to include in such compositions one or more peptides, in particular peptides that are naturally secreted by the pancreas together with insulin in [non- iabetics] non-diabetics. Such peptides are herein referred to as "insulin-related peptides".

Please replace the paragraph at page 12, lines 7-13, with the following paragraph:

In an alternative embodiment, the insulin and/or insulin analog [are] is replaced by an insulin mimetic material that functions to [actiavte] activate the human [inslin] insulin receptor. Examples of suitable insulin [mimentic] mimetic materials are shown and described in U.S. Provisional Patent Application Serial No. 60/135,278 filed on May 21, 1999 and entitled "Device and Method for Infusion of Small Molecule Insulin Mimetic Materials, which is specifically incorporated by reference herein end forms a part of this disclosure.

APPENDIX: VERSION WITH MARKINGS
TO SHOW CHANGES MADE TO THE CLAIMS

IN THE CLAIMS

Please cancel claims 10, 15, 16, 18, 24, 53, 55-57 and 69-70, without prejudice to Applicants' right to pursue the subject matter of these claims in another application. Please amend claims 1, 7, 12, 17, 19-21, 33, 35-37, 41, 46, 48-51, 58-59, 66 and 71 as follows:

1. (Amended) A pharmaceutical composition comprising: [at least two of agents i) - iii), wherein]

agent i) [is] selected from the group consisting of an insulin, an insulin analog, a physiologically active fragment of said insulin and a physiologically active fragment of said insulin analog,

agent ii) [is] selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulin-related peptide analog fragment, and

agent iii) [is] an insulin sensitizer.

7. (Amended) The composition of claim 6 wherein said peptide is selected from the group consisting of C-peptide, glucagon-like peptide-1 (GLP-1), amylin, insulin-like growth factor-1 (IGF-1) and IGF-1 bound to binding protein 3.

12. (Amended) The composition of claim [10] 1 further comprising a pharmaceutically acceptable non-ionic surfactant.

17. (Amended) The composition of claim [16] 1 comprising about 0.5 to about 40 mg/ml of agent i) and about 0.05 to about 12 mg/ml of agent iii).

19. (Amended) The composition of claim [18] 1 comprising [comprising] about 0.05 to about 12.5 mg/ml of agent ii) and about 0.05 to about 12.5 mg/ml of agent iii).

20. (Amended) The composition of claim 1 comprising two or more compounds of agent[s] i), two or more compounds of agent ii), or two or more compounds of agent iii).

21. (Amended) A pharmaceutical composition comprising

i) at least one agent selected from the group consisting of an insulin, an insulin analog, a physiologically active insulin fragment and a physiologically active insulin analog fragment and

ii) at least one agent selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulated-related peptide analog fragment, and

iii) an insulin sensitizer;

wherein said agent ii) comprises a hydrophobic portion that is coated with a pharmaceutically acceptable non-ionic surfactant.

33. (Amended) A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim [10] 1.

35. (Amended) A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim [15] 14.

36. (Amended) A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim [16] 17.

37. (Amended) A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim [18] 19.

41. (Amended) A method of treating diabetes comprising the step of administering to a patient in need of such treatment [at least two] pharmaceutical compositions a)-c), wherein

composition a) comprises

i) at least one agent selected from the group consisting of an insulin, an insulin analog, a physiologically active fragment of said insulin and a physiologically active fragment of said insulin analog, and

ii) a pharmaceutically acceptable carrier,

composition b) comprises

i) at least one agent selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulin-related peptide analog fragment, and

ii) a pharmaceutically acceptable carrier, and

composition c) comprises

i) an insulin sensitizer, and

ii) a pharmaceutically acceptable carrier.

46. (Amended) The method of claim 41 wherein compositions a) and b) are administered to said patient using a single delivery device.

48. (Amended) The method of claim 41 wherein compositions a) and c) are administered to said patient using a single delivery device.

49. (Amended) The method of claim 41 wherein compositions b) and c) are administered to said patient using a single delivery device.

50. (Amended) The method of claim 41 wherein compositions a), b) and c) are administered to said patient using a single delivery device.

51. (Amended) A method of making a pharmaceutical composition useful in treating diabetes, said method comprising the step of combining [at least two of] agents i) - iii), wherein

agent i) is selected from the group consisting of an insulin, an insulin analog, a physiologically active fragment of said insulin and a physiologically active fragment of said insulin analog,

agent ii) is selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulin-related peptide analog fragment, and

agent iii) is an insulin sensitizer.

58. (Amended) A method of treating diabetes and at least one side effect thereof which comprises the step of administering to a patient in need of such treatment a pharmaceutical composition comprising

a) at least one agent selected from the group consisting of an insulin, an insulin analog, a physiologically active insulin fragment and a physiologically active insulin analog fragment,

b) at least one agent selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulin-related peptide analog fragment, wherein said agent is effective in treating said side effect, [and]

c) a pharmaceutically acceptable non-ionic surfactant, and

d) an insulin sensitizer.

59. (Amended) A pharmaceutical composition comprising [at least two of] agents i) - iii), wherein

agent i) is selected from the group consisting of an insulin mimetic material,

agent ii) is selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment, and a physiolgically active insulin-related peptide analog fragment, and

agent iii) is an insulin sensitizer.

66. (Amended) The composition of claim 59 comprising about 1.5 to about 40 mg/ml of agent i), [and] about 1.5 to about 40 mg/ml of agent ii), and about 0.05 to about 12.5 mg/ml of agent iii).

71. (Amended) The composition of claim 59 comprising two or more compounds of agent[s] i), two or more compounds of agent ii) or two or more compounds of agent iii).